REMARKS/ARGUMENTS

1. Response to Notice of Non-Compliant Amendment

In the Notice of Non-Compliant Amendment, the Examiner indicated that claim 16 should have been listed as "currently amended." Applicants provide this further Amendment in order to present claim 16 as "currently amended" as requested.

Applicants note that claim 16, as presented, corresponds to claim 16 as it was amended in the Amendment dated January 26, 2005. Applicants' prior Amendment dated August 19, 2005 inadvertently did not list claim 16 as it was amended in the Amendment dated January 26, 2005. The present Amendment amends claim 16 so that claim 16 is the same as it was amended by the Amendment dated January 26, 2005.

2. Rejection Under 35 USC 112, First Paragraph

The Examiner rejects claims 1-7, 16, 21-26, 31-36, 38, 40, 42, 45, and 48-57 under 35 USC 112, First Paragraph on the grounds that "non-iterative manner" is new matter not disclosed in the specification as filed.

As Applicants noted in the previous Amendment, "it is through the performance of the operations of the second computer executable logic to compare the results of the first computer executable logic that the best search model is identified." In this regard, the presently claimed invention distinguishes Kissinger which **iteratively** optimizes the molecular replacement search conditions for a given search model using EPMR solely. Applicants believe that this distinction is made clear in the claims by the recitation of first and second computer executable logics and thus the phrase "in a non-iterative manner relative to the operation of the first computer executable logic" is descriptive but not necessary to the claims. Applicants delete from the claims this phrase which forms the basis of the Examiner's rejection. Withdrawal of this ground of rejection is therefore respectfully requested in view of the amendments to the independent claims.

3. **Rejection Under 35 USC 103(a)**

The Examiner continues to maintain his rejection of claims 1-7, 16, 21-26, 31-36, 38, 40, 42, 45, and 48-57 under 35 USC 103(a) on the grounds that the claims are rendered obvious over Kissinger, et al. (Acta Crystallographica Section D, Biological Crystallography, 1999, D55, 484-491).

A. Kissinger's subsequent publications evidence that Kissinger, et al. is not an enabling reference with regard to search models based on a group of different biomolecules.

In the Office Action, the Examiner acknowledges that "Kissinger reference does not teach use of a group of biomolecules for multiple searches at once." Instead of therefore accepting that Kissinger does not enable the use of search models based on a group of different biomolecules and does not teach how search models based on a group of different biomolecules would be used, the Examiner states that "the reference clearly addresses such parallel approach of using multiple search models as one of **potential** enhancement of EPMR." Applicants emphasize **"potential"** because the Kissinger reference's teaching is only of the **potential** to enhance EPMR. However, without any teaching how to achieve that potential, the reference cannot be said to enable that potential.

In support of Applicants' position that Kissinger, et al. is not enabling as to the use of search models based on a group of different biomolecules, the Examiner's attention is drawn to a 1998 abstract by Kissinger, et al. entitled "Rapid Automated Molecular Replacement Using an Evolutionary Search Algorithm (WO102) *("1998 Abstract")* **[Exhibit A]** which teaches the use of only a single search model. The 1998 Abstract appears to be related to and preannounce the Kissinger, et al. reference relied upon by the Examiner. Three years later, in April 2001, Kissinger publishes an abstract for the same conference entitled "Automated Molecular Replacement" (WO299) *("2001 Abstract")* **[Exhibit B]** which teaches the advancement of the EPMR method to allow "multiple search models to be evaluated." Reading the two abstracts together, one recognizes that EPMR was not

enabled by Kissinger as of 1999 for using search models based on a group of different biomolecules. Applicants note that the 2001 Abstract only announces the enhancement but does not disclose any details regarding how the enhancement was achieved.

Applicants' assessment that Kissinger, et al. is not enabling as to the use of search models based on a group of different biomolecules is substantiated by Version 2.5 of the EPMR manual (copyright date 2001) *("2001 EPMR Manual")* **[Exhibit C]** which teaches at page 2 that

> because of the stochastic nature of the optimization process, you will not get the correct solution on every run, even with a very good search model. The success rate is usually very high **assuming AN adequate model**, but you probably want to try at least 10 runs if you have a difficult problem. For **search models that are poor** and at the limit of detectability, **the search efficiency can be quite low**. If you have a molecular replacement problem that has not yielded a solution by any other means, a reasonable **last resort is to set up EPMR to do as many runs as your patience and computing resources will allow**. As long as the true solution represents the global maximum in the correlation coefficient between Fo and Fc, even if by the slimmest of margins, EPMR will eventually find it.

As can be seen from the above passage, the 2001 EPMR Manual clearly teaches that "an adequate model" is needed because the search efficiency is quite low for poor search models. The 2001 EPMR Manual further teaches that EPMR may be used as a "**last resort**" using a poor model, provided the researcher is willing to do "as many runs as your patience and computing resources will allow." Based on Kissinger's own description of EPMR in 2001, one of ordinary skill would not read the 1999 Kissinger, et al. reference as being viable for screening search models derived from a group of different biomolecules through EPMR to identify a preferred search model from among the group for molecular replacement. In view of the 2001 EPMR Manual, this use of EPMR would logically be well beyond the user's "last resort" in relation to "patience and computing resources." Kissinger, et al. read in combination with the 2001 EPMR Manual thus teaches away from the use of EPMR (as taught in the Kissinger, et al. reference) in combination with poor search models.

In direct contrast to Kissinger, et al., the present invention teaches how to advantageously use poor search models in conjunction with performing molecular replacement. Specifically, these poor search models create a baseline whereby the biomolecules that serve as excellent search models stand out. In this regard, the first computer executable logic performs molecular replacement using search models for a group of structures of different biomolecules and the second computer executable logic performs the comparison whereby the biomolecules that serve as good search models stand out. As taught in the Specification, page 14, line 25 – page 15, line 10,

> comparing molecular replacement solutions allows one to determine that a given search model is superior to the other search models tested. More specifically, given that very few search models will have significant structural identity with the biomolecule or biomolecule complex whose structure is being solved, comparison of molecular replacement solutions according to the present invention allows one to establish a background correlation level based on a statistically significant number of structures that do not match. This makes it possible to readily identify superior search models by looking for a significantly greater correlation than the background correlation level. By being able to evaluate how much superior a given search model is relative to other search models, one is also able to infer whether any of the search models have significant structural identity with the biomolecule or biomolecule complex whose structure is being solved. This thus allows one to select which search model to use as the search model for molecular replacement.

The Examiner points out correctly in the Office Action that "EPMR is a preferred method of performing molecular replacement in the instant invention." However, whereas EPMR is the sole teaching in Kissinger, et al., EPMR is only a subcomponent of the present invention that may be used as part of the first computer executable logic. EPMR does not form any part of the second computer executable logic which compares molecular replacement results. The use of a prior art subcomponent (EPMR) does not render an invention unpatentable if such invention further uses other components (i.e., the second computer executable logic) not taught in such prior art or if the invention uses the prior art subcomponent in a manner that it has not been used before.

The Examiner also points out in the Office Action that EPMR compares molecular replacement solutions among multiple EPMR runs using the **same** search model. The Examiner evidently likens this comparison to the second computer executable logic of the present invention. However, the Examiner mistakenly assumes that comparing molecular replacement solutions using the **same** search model is equivalent and interchangeable with comparing molecular replacement solutions using the search models based on different biomolecules. Applicants submit that this leap in logic is unfounded. As Applicants describe herein, that concept is not supported by Kissinger, et al., is contradicted by the 2001 EPMR Manual and is shown to be a separate, further invention based on the 2001 Abstract.

As noted in the Specification at page 14, lines 27-29, "very few search models will have significant structural identity with the biomolecule or biomolecule complex whose structure is being solved." Thus, in direct contrast to the 2001 EPMR Manual which prefers to avoid the use of a poor search model, the present invention uses the second computer executable logic to use poor structural matches to its advantage by establishing "a background correlation level" and enabling superior search models to be readily identified "by looking for a significantly greater correlation than the background correlation level." In fact, as noted at in the Specification at page 15, line 2, it is best to have "a statistically significant number of structures that do not match."

As Applicants have stated before, Kissinger, et al. admits that only early (undisclosed) experiments were performed that suggest that EPMR might be useful with multiple search models. No teaching regarding how these experiments were conducted is provided. Applicants urge the Examiner to accept that this alone is not an enabling teaching. The subsequent 2001 EPMR Manual substantiates Applicants' assessment by teaching that a poor structure model can be used with low efficiency "as a last resort." The 2001 Abstract further substantiates Applicants' assessment by announcing the scientific development of an improvement to EPMR that allows multiple search models to be evaluated (without teaching how). In view of the further evidence provided by Applicants regarding the interpretation of Kissinger, et al. Applicants respectfully request that the

Examiner acknowledge that the second computer executable logic is not taught by Kissinger, et al. and withdraw the pending rejection for obviousness.

B. The Examiner mischaracterizes the claimed invention as competing in the same manner as Kissinger.

In support of the Examiner's rejection for obviousness, the Examiner states at page 5-6 that "second, by competing the reference understands rank ordering of candidates by their scoring and **discarding** lower scoring individuals, i.e., the **same method steps** as in the instant method."

To be clear, Applicants do not "discard" lower scoring individuals in the manner of Kissinger, et al. and this is not the same method step as what is being claimed.

Applicants purposefully distinguish the first computer executable logic which performs molecular replacement searches using a group of structures of different biomolecules from the second computer executable logic which compares the results (does not discard the results!) of the first computer executable logic. Applicants submit that the operation of the second computer executable logic to compare results from the molecular replacement searches where different biomolecules are used in order to pick a search model is a method step that is not an evolutionary competition as taught by Kissinger, et al.

Significantly, Kissinger, et al. discards lower scoring molecular replacement solutions for improved molecular replacement solutions where the **same** underlying biomolecule is used throughout. Kissinger, et al. does not "discard" lower scoring molecular replacement among different biomolecules. In fact, Kissinger, et al. could not discard a molecular replacement solution for one biomolecule over a molecular replacement solution for another biomolecule because Kissinger, et al. does not teach how to make comparisons across different biomolecules. Rather, it is only the present invention that teaches how to make comparisons of search models across different biomolecules. Kissinger, et al. only teaches how to draw comparisons between molecular replacement solutions that employ the same biomolecule.

In view of these further distinctions, the present invention cannot be said to "**discard** lower scoring individuals" or employ the same method steps as Kissinger, et al.

C. The Examiner misinterprets Kissinger, et al. in regard to "single or multiple molecules".

The Examiner states at page 6 (first full paragraph) of the Office Action that

> the reference both teaches that the method can utilize either single or multiple molecules (see paragraph bridging columns on p. 490) and suggests that instead of single search model, a set of structural models can be used (p. 490, last paragraph).

With this statement, the Examiner is evidently misinterpreting the teaching of Kissinger, et al. with regard to "single or multiple molecules in the asymmetric unit."

By way of background, protein crystals may form a crystal lattice where each asymmetric unit of the crystal has a single molecule or where the asymmetric unit has multiple molecules. The molecule in that asymmetric unit is **NOT** the biomolecule used in the search model. Rather, it is the molecule whose crystal structure is to be solved (i.e., the target molecule). Hence, Kissinger, et al. teaches that EPMR can be used to solve the structure of a target molecule where the crystal of the target molecule has a single molecule in the asymmetric unit or multiple molecules in the asymmetric unit. The paragraph bridging columns on p. 490 regarding the number of molecules in the asymmetric unit is thus wholly unrelated to the last paragraph of p. 490 regarding the use search models from different biomolecules. Accordingly, contrary to the Examiner's assertion, paragraph bridging columns on p. 490 does not further the Examiner's assertion that a set of structural models can be used.

D. **Independent Claims 53-55.**

Based on the Examiner's statement in regard to independent claims 53-55, Applicants suspect that the Examiner has not yet fully appreciated independent claims 53-55.

The point of independent claims 53-55 is not to find a molecular replacement "**and then**... use such molecular replacement to identify the structure of the target molecule." Rather, as specified in independent claim 53-55, the present invention allows one to **predict** which biomolecule search model will produce a molecular replacement solution that is superior to the molecular replacement solutions produced by the other biomolecule structures in the group **and then** use that search model to perform molecular replacement.

Advantageously, this prediction can be made **without** having to first discover the best molecular replacement solution itself. Rather, once this prediction is made, that biomolecule search model can be used to solve the structure of the target molecule.

Kissinger, et al. by contrast, is only useful for taking a given biomolecule structure and optimizing the molecular replacement solution that can be produced using that biomolecule structure. Kissinger, et al. does not support a process whereby the best biomolecule search model from among a group of biomolecules is selected without evolving that search model to the best molecular replacement solution.

As noted above, Kissinger, et al. teaches the importance of using the best search model possible. This is because it is much more efficient to evolve an *excellent search model* to the best molecular replacement solution that search model can produce than it is to evolve a *poor search model* to the best molecular replacement solution that search model can produce. See 2001 EPMR Manual. This is why Kissinger, et al. teaches to avoid using poor search models.

Kissinger, et al. **does not** teach how to compare search models based on different biomolecules so that **after** the search models are compared, the best search model can be identified. By providing a means for identifying the best biomolecule search models from

among a group of different biomolecule search models without having to find the best molecular replacement solution at the same time, the present invention fills a gap not addressed by Kissinger, et al. With the ability to predict which biomolecule search model is the best, superior search models can be used to solve the structure, for example using EPMR to solve the structure. Given that EPMR's efficiency is dependent upon the quality of the search model, one can see that the present invention makes EPMR more efficient by identifying the very best search models to use with EPMR.

The Examiner is therefore respectfully requested to recognize the ability of the present invention to prediction which biomolecule search model to use as something not taught or suggested by Kissinger, et al.

Applicants note that the above discussion regarding the Examiner's misinterpretation of independent claims 53-55 should not be limited to these independent claims but rather is applicable to the other pending claims. Applicants hope that the Examiner's review of this Amendment will help the Examiner to more fully appreciate the distinctions of the claimed invention over Kissinger, et al. that are so apparent to Applicants.

E. **Dependent Claims 4-7, 14, 16, 22-25, 31-34, 36.**

Applicants wish to draw the Examiner's attention to dependent claims 4-7, 14, 16, 22-25, 31-34, and 36 which claim the use of search models based on multiple different biomolecules (claim 14), the use of search models based on structurally distinct biomolecules (claims 16 and 36) and the use of search models based on multiple different biomolecules where the molecular replacement results have a broad distribution thereby evidencing which are exceptional search models (Claims 4-7, 22-25, and 31-34).

In the Office Action, the Examiner states with regard to the dependent claims that "absent some teaching to the contrary, however, the determination of such criteria is within the skill of the ordinary worker."

As noted above, the 2001 EPMR Manual teaches to use the best search model possible with EPMR. Practicing the dependent claims effectively forces one to use inferior

search models by essentially insuring that a poor search model is utilized. Hence, these dependent claims are in direct **contradiction** to the teaching of the 2001 EPMR Manual These claims both further evidence the inventiveness of the present invention and separately serves as points of novelty. The Examiner is respectfully requested to recognize the further patentability these dependent claims convey.

F. **Conclusion.**

Applicants submit that the claimed invention distinguishes Kissinger, et al. by (a) using search models based on different biomolecules; and (b) having a second computer executable logic draw comparisons between solutions generated using search models based on different biomolecules. The teaching of Kissinger, et al. at most makes a suggestion that different biomolecules may some day be used in some way in conjunction with EPMR. However, Kissinger, et al. provides no teaching or suggestion how that could be accomplished. Extrinsic evidence to Kissinger, et al. demonstrate that EPMR as of 2001 was poorly adapted to utilize poor models let alone models from different biomolecules and that Kissinger considered his 2001 Abstract reporting the use of different biomolecules to be a meaningful advancement over the state of the art. In total, Applicants submit that Kissinger, et al. clearly does not render the present invention obvious.

Applicants encourage the Examiner to telephone the undersigned should the Examiner have any questions in order to avoid the necessity for this application to be resolved on appeal.

Respectfully submitted,
Takeda San Diego, Inc.

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By: _____
David J. Weitz, General Counsel
& V.P. of Intellectual Property
Reg. No. 38,362

Customer No. 32793
Takeda San Diego, Inc.
10410 Science Center Drive
San Diego, CA 92121
Telephone: (858) 622-8528
Facsimile: (858) 550-0992